REMARKS

Applicant thanks Examiner Staples for his time and consideration of the present application during the telephonic interview with the undersigned on January 20, 2010.

During the interview, the applied references were discussed. Also, a sample concordance correlation coefficient for the previously filed data of January 22, 2009 was presented, along with a new table comparing the sensitivity and specificity for the claimed and new primers. Also new evidence in support of non-obvious was discussed. Examiner Staples suggested filing a new declaration directed to the previously filed experimental data, the sample concordance correlation coefficient, the new data table, and the new evidence in a response to the Official Action.

Examiner Staples that such a declaration and new evidence would require further consideration and/or search, and, thus, this response is filed with a Request for Continued Examination.

Reconsideration of the present application is respectfully requested.

Status of the Claims

Claim 1 is amended to remove "pre-cancerous lesions".

Claims 1, 9, 10, and 12 remain pending.

Claim Rejections-35 USC 112

Claims 1, 9 and 10 were rejected under 35 USC 112, second paragraph, for being indefinite. This rejection is traversed for the reasons below.

The term "pre cancerous lesion" has been removed from claim 1.

Therefore, pending claims 1, 9, 10 and 12 are definite, and withdrawal of the rejection is respectfully requested.

Claim Rejections-35 USC 103

Claims 1, 9 and 10 were rejected under 35 USC 103(a) as allegedly being unpatentable over SHUBER, KMIEC, ALBERTSON, and BUCK. This rejection is respectfully traversed.

The Official Action relies on BUCK (page 3 and pages 10 - 11) in support of the position that equivalence has been shown among different primers from the same DNA region.

BUCK's paper, however, deals with equivalence among primers with regard to their use for the sequence analysis of those regions. As already discussed in the reply filed January 22, 1009, the characterization of genomic DNA through sequencing methods is different from the quantification of genomic DNA

molecules/fragments described in our patent application. For sequencing analysis, a qualitative (sequence reading for gene discovery, mutation analysis, SNPs etc.) rather than accurate quantitative characterization of DNA fragments can only be made. This cannot be influenced by different primers spaced in adjacent nucleotides.

The Official Action, quoting BUCK, replied to applicant's arguments that different primers do not give different results, but there does not appear to be an appreciation of the fact that applicant's test and BUCK's study had different objectives.

In BUCK's study the researchers perform a Qualitative, sequencing evaluation, whereas applicant's test Quantitative. The possibility of reading the genomic DNA sequence is not directly correlated with that of quantifying the DNA molecules present in the samples or of determining their integrity.

The quantity of amplified DNA for each analyzed region, however, is the key element of applicant's test. In fact, it is the quantity of non fragmented DNA amplified by applicant's method, not the sequencing analysis, which determines the results and makes it possible to identify the neoplastic lesions. For these reasons BUCK's paper cannot be used to reject the present claims.

Furthermore, BUCK uses high quality genomic DNA extracted from specimens for which the quality and quantity of

DNA recovery is generally good or very good. This is another substantial difference between BUCK and the claimed invention. The quality and quantity of genomic DNA that can be extracted from stool as claimed, however, is generally poorer, as evidenced by Loktionov in International Journal of Cancer 120:2281-2289 provided in the Appendix. Thus, the quality of DNA influences results and also the possibility of obtaining similar results using different amplification conditions, e.g. different primers.

Accordingly, it is impossible to make a direct comparison with the primers used in BUCK's article, especially if the above considerations about the DNA used for BUCK's tests are taken into account. The different data obtained using the claimed primers and respectively the new primers, as reported in the previous reply (and revised in the new declaration in the appendix), confirm the importance of the primers used and are not disproved by the position of the Official Action based on BUCK's study.

Specifically, the Examiner's attention is respectfully directed to Table 1 of the Declaration filed under Rule 132 in the present Appendix. As shown below the data, the sample concordance correlation coefficient (p_c) is 0.0456, which confirms that these two approaches based on different primers, but using the same samples analyzed at the same time, produces different values. Moreover, as further evident by Table 2 in the

declaration, the test sensitivity and specificity are not the same when different primers are used.

As to the primary reference, SHUBER, the analysis method used is different and does not give the same results as those obtained by the claimed invention, as evidenced by the article Neoplasia 6:536-540, 2004 provided in the Appendix. This article relates to applicant's own study.

In the study, applicant demonstrated that a method based on agarose gel, i.e., as described by SHUBER, and fluorescence quantization determines substantially different results in terms of accuracy in identifying neoplastic lesions. This difference is not obvious and was not considered in SHUBER.

The dynamic range of the two systems is one of the most important characteristics needed in order to obtain good discrimination between cancer patients and healthy individuals. In fact, even when the same approach is used (e.g., agarose gel electrophoresis as used by SHUBER), different DNA markers can give different results in terms of dynamic range and of the possibility of distinguishing between samples with similar but not identical levels of long DNA molecules. The ethidium bromide used by SHUBER (line 31) is probably the least effective reagent for this type of analysis (as generally known in the prior art, e.g., Cancer Research 58:3957-64, 1998; Analytical Biochemistry 18:197-208, 1989; PCR Methods and Applications 4:234-238, 1995). Indeed, the article from Neoplasia discloses that in using

"fluorescent methods", as opposed to the "ethidium bromide method", sensitivity improvement of about 30% was obtained.

The ability to discriminate between very similar quantities is fundamental in order to correctly identify patients with neoplastic colorectal disease, as evidenced by Neoplasia 6:536-540, 2004 provided in the appendix. Applicant's approach significantly adds to the accuracy already obtained by SHUBER, a fact that SHUBER did not take into consideration, erroneously stating that various methodological approaches may determine equivalent results.

Neither KMIEC nor ALBERTSEN is able to remedy these deficiencies of SHUBER and BUCK for reference purposes.

Therefore, in view of the above, the claimed method, or test, is unobvious and provides unexpected superior results to those suggested by the proposed combination.

Conclusion

In view of the foregoing remarks, this application is in condition for allowance at the time of the next Official Action. Allowance and passage to issue on that basis is respectfully requested.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following item(s):

-a 37 CFR 1.132 Declaration by Daniele Calistri, dated February 12, 2010.

- Daniele Calistri et al., Detection of Colorectal Cancer by a Quantitative Fluorescence Determination of DNA Amplification in Stool, Neoplasia Vol.6, No. 5, pp. 536-540, 2004.

- Loktionov, Cell exfoliation in the human colon: Myth, reality and implications for colorectal cancer screening, Int J Cancer 120:2281-2289(2007).